Comparison of the solution structures of (+)- and (-)-*trans-anti*-5-methylchrysene-DNA duplex adducts.

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The tumorigenicity of the environmental carcinogen chrysene is greatly enhanced by methyl substitution at the 5-position. 5-Methylchrysene can be metabolically activated to isomeric (+)- and (-)-1,2-diol 3,4-epoxides (*syn* and *anti*-5-MeCDE), each of which exhibit different extents of deleterious consequences to the cell. Both (+)- and (-)-*anti*-5-MeCDE bind primarily to the N^2 group of guanine by *trans* addition to C4 ((+)- and (-)-*trans*-[MC]dG); and, the formation of these adducts is believed to be critical in initiating mutations and cancer. The (+)-*anti*-5-MeCDE isomer is more mutagenic and carcinogenic than the (-)-*anti* enantiomer; in order to correlate these differences in activities with structure, a combined NMR-molecular mechanics approach was used to determine the solution structures of the major (+)- and (-)-*trans*-[MC]dG adducts in the sequence context of d(CCATC^{MC}GCTCC)·d(GGTAGCGATGG). The chrysenyl ring in the structure of the (-)-*trans* adduct is located in the minor groove of a B-DNA duplex, pointing toward the 3'-end of the modified strand. The methyl group is inserted into the helix between the modified and 3'-side G-Cs pairs, bending the DNA by ~47° but otherwise not perturbing the DNA. In contrast, the structure of the (+)-*trans* adduct exhibits conformational heterogeneity with a possible hinge point located to the 5'-side of the modification site. Supported by NIH & DOE. This work was performed under the auspices of the U.S. DOE by LLNL under contract no. W-7405-ENG-48 and by ORNL under contract no. DE-AC05-84OR21400.